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Tobacco Harm Reduction & Reduced-Risk Products

Andrei Ghizdavescu
Philip Morris International
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Creating a New Category: Reduced Risk

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Reduced-Risk Products ("RRPs") is the term we use to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

We have a range of RRPs in various stages of development, scientific assessment, and commercialization.

Because our RRPs do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.

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Tobacco Harm Reduction

The Objective Is Harm Reduction

- Smoking is addictive and causes a number of serious diseases
- Worldwide, it is estimated that more than 1 billion people will continue to smoke in the foreseeable future*

Population Harm Reduction = **Reduced-Risk Products** x **Product Adoption and Usage**

- Successful harm reduction requires that adult smokers who would otherwise continue to smoke be offered a range of satisfying, scientifically substantiated, reduced-risk products to which they can switch completely

- http://www.who.int/tobacco/publications/surveillance/reportontrendstobaccosmoking/en/index4.html.
- Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013)
- Note: Reduced Risk Products ("RRPs") is the term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking.

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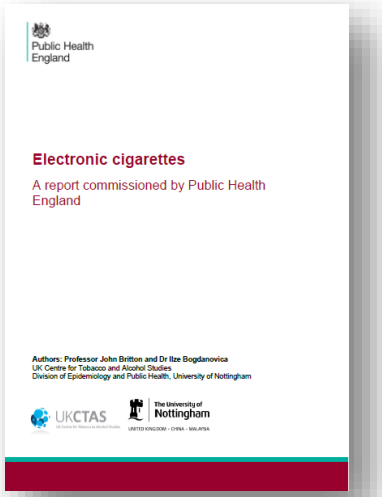
Nicotine Is Not the Primary Cause of Smoking-Related Diseases….



May 2014, Public Health England :
"[…] **Nicotine does not cause serious adverse health effects** such as acute cardiac events, coronary heart disease or cerebrovascular disease, and is **not carcinogenic**. The doses of nicotine delivered by electronic cigarettes are therefore extremely unlikely to cause significant short or long-term adverse events.[…]"

July 2017, FDA Commissioner Dr. Scott Gottlieb :
"[…] **nicotine in itself is not responsible** for the cancer, the lung disease and heart disease that kill hundreds of thousands Americans every year. […] it is the **other chemical compounds** in tobacco and in the **smoke created by setting the tobacco on fire** that directly cause illness and death."

FDA U.S. FOOD & DRUG ADMINISTRATION

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A Growing Number of Countries Are Recognizing the Benefit of Better Alternatives

Governments recognize the potential benefits of smoke-free alternatives for public health

FDA

*"…**new product innovations** could make a lot of sense and **help people transfer off cigarettes**"*

- Scott Gottlieb, Commissioner Food & Drug Administration

Public Health England

*"help people to quit smoking by **permitting innovative technologies that minimise the risk of harm**" / "maximise the availability of safer alternatives to smoking"*

"The available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes and more harmful than e-cigarettes."

MINISTRY OF HEALTH
MANATŪ HAUORA

*"**heat-not-burn**, snus, moist snuff, dissolvables and inhaled nicotine **may be significantly safer than cigarettes**."*

- Nicky Wagner, Associate Health Minister

PMI's Reduced-Risk Product Portfolio

Heated Tobacco Products

PLATFORM 1

ELECTRICALLY HEATED TOBACCO PRODUCT (EHTP) OR TOBACCO HEATING SYSTEM (THS)

PLATFORM 2

CARBON-HEATED TOBACCO PRODUCT (CHTP)

Products Without Tobacco

PLATFORM 3

NICOTINE DELIVERY SYSTEM

PLATFORM 4

E-VAPOR PRODUCTS

Note: The RRPs depicted are subject to ongoing development; therefore, the descriptions are illustrative and do not necessarily represent the latest stages of product development.

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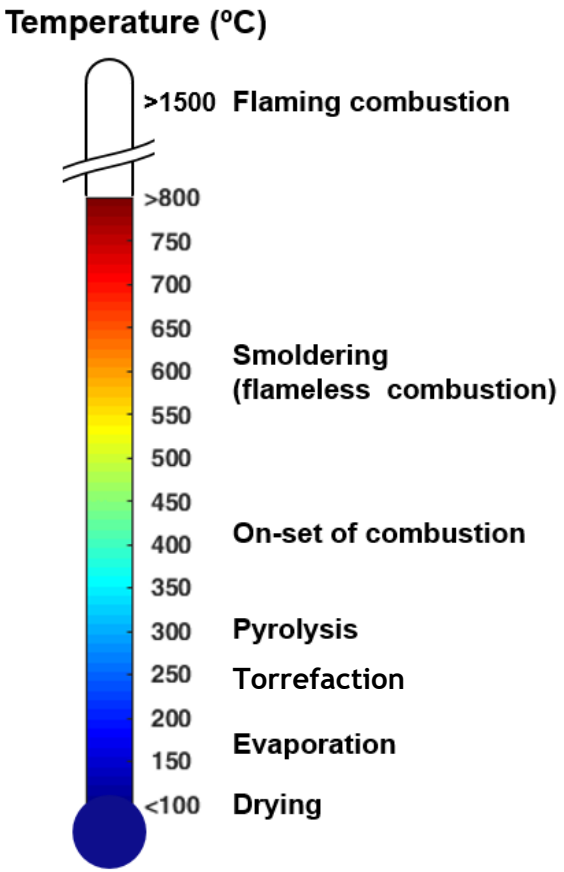
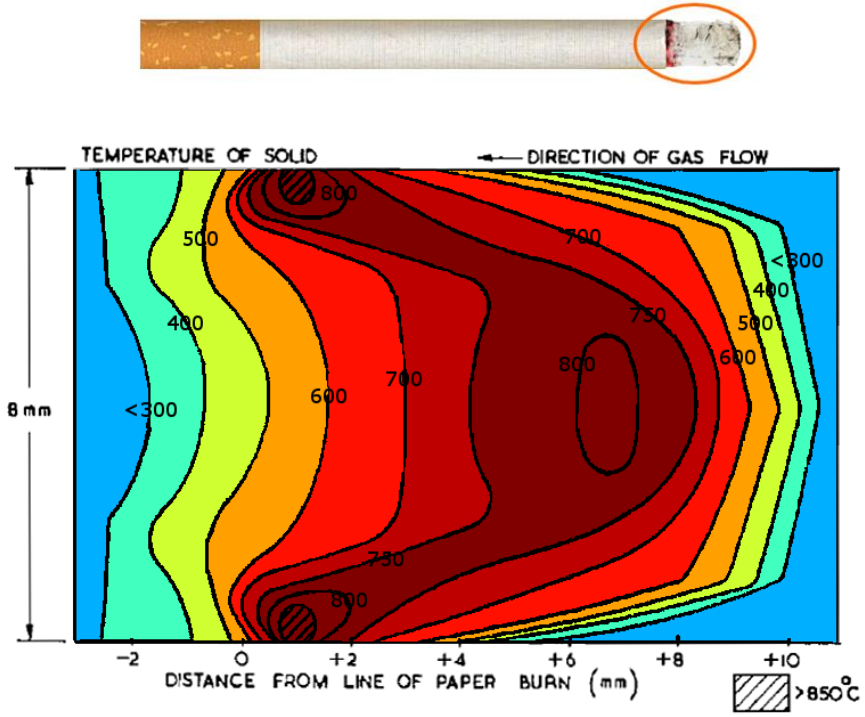
Combustion

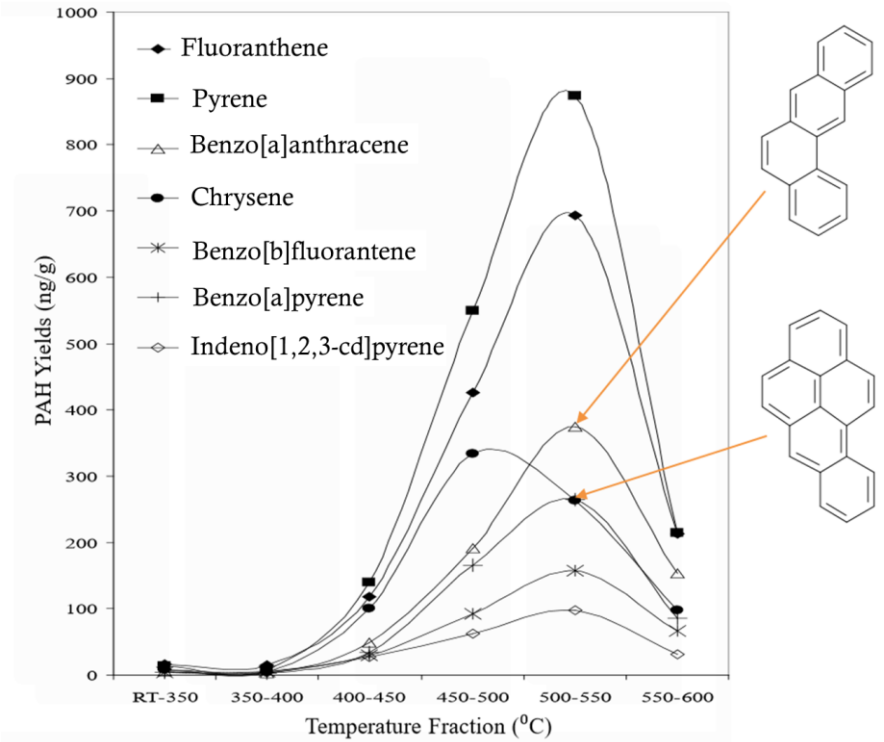
Elimination of Combustion Is Key

Scientific studies have shown that as the temperature of tobacco increases, the levels of harmful chemicals formed increase





Source: Baker R. R., 1975, Temperature variation within a cigarette combustion coal during the smoking cycle, High Temp. Sci., 7, 236-247. Coloration by PMI.



Source: McGrath, T.E., Wooten, J.B., Chan W.G. and Hajaligol, M.R., 2007, Formation of polycyclic Aromatic Hydrocarbons from Tobacco: the "Link" between Low Temperature Residual Solid and PAH Formation, Food and Chemical Toxicology, 45,6,1039-1050

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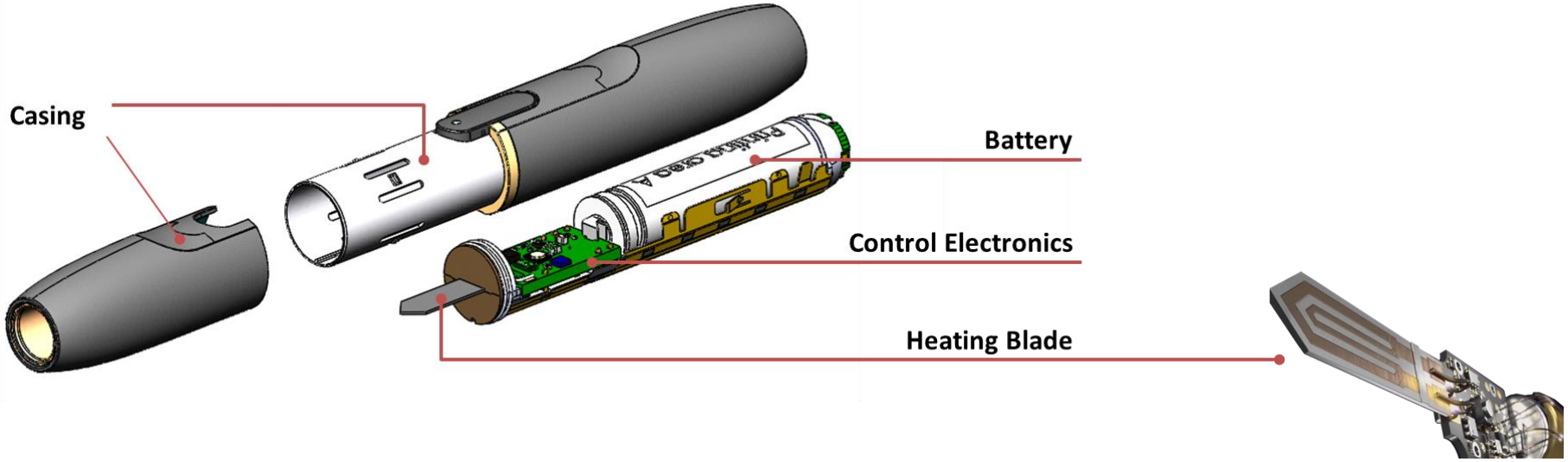
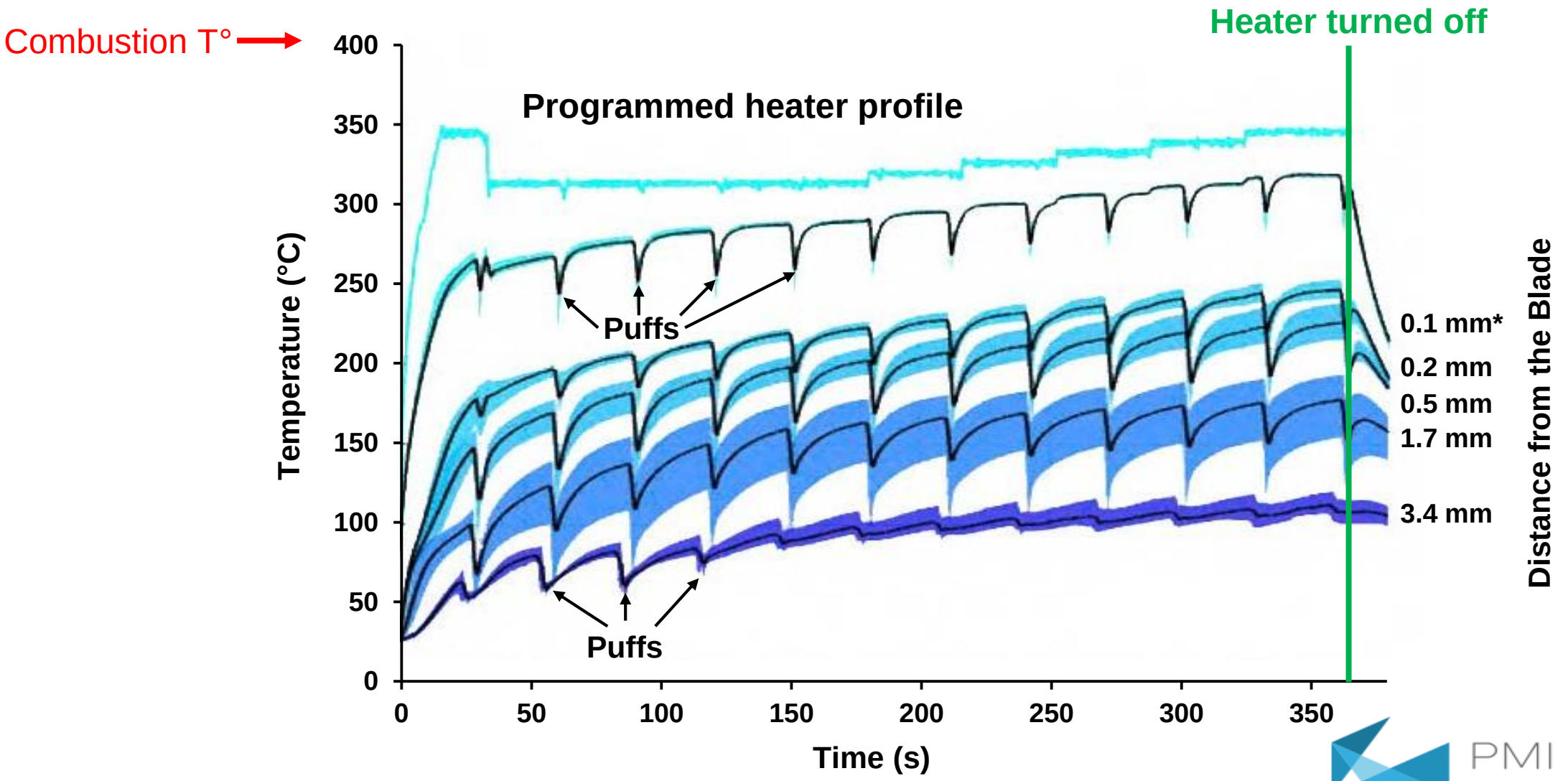
The Tobacco Heating System 2.2

How THS Works

- The Tobacco Heating System (THS, marketed as *IQOS*) is designed to heat tobacco without burning and smoke – the maximum temperature reaches approximately 350°C.
- In contrast, cigarettes can exceed 850°C during puffs.
- THS is designed as an alternative to cigarettes for current adult smokers who would otherwise continue to smoke.



THS Temperature Profile



* Radial position of thermocouple relative to the surface of the heater

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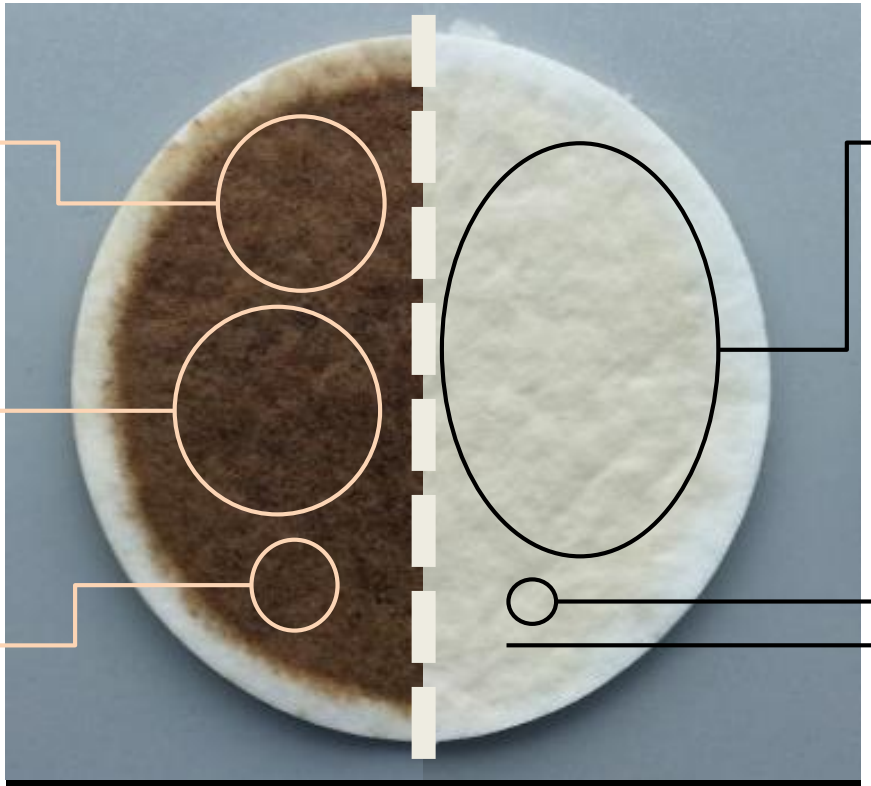
Smoke Is Different from Tobacco Vapor (Aerosol)

Water and glycerin form 50% of smoke mass

HPHCs

Contains carbon-based solid particles



Water and glycerin form 90% of aerosol mass

HPHCs reduced by >90%

No carbon-based solid particles

Smoke and aerosol were collected on a Cambridge filter pad using the Health Canada Intense smoking regime

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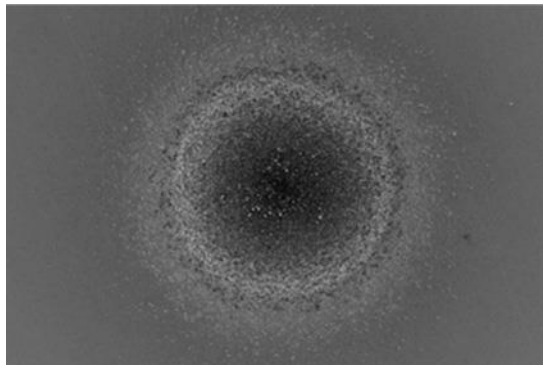
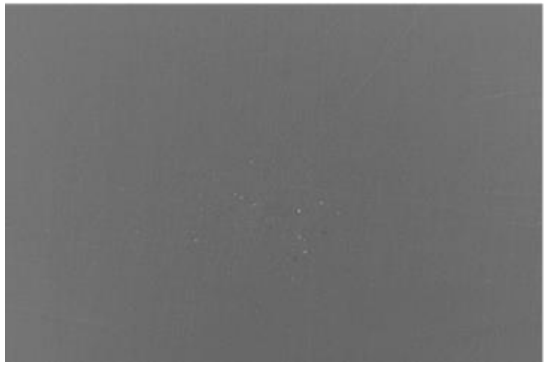
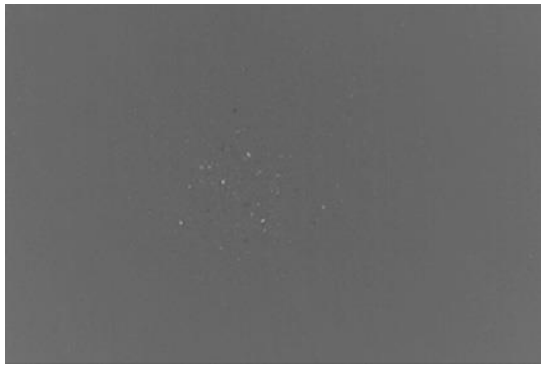


Cigarette smoke

Carbon-based nanoparticles
Median diameter = 75 nm
Amount: $6x10^{11}$ particles ~= 0.7 mg*



Blank (Air)



THS aerosol

No solid particles

Scanning electron microscopy images of the collected smoke/aerosol

* Under the Health Canada Intense smoking regime.

Pratte et al. Investigation of solid particles in the mainstream aerosol of the Tobacco Heating System THS2.2 and mainstream smoke of a 3R4F reference cigarette. *Hum. Exp. Toxicol*, 2017; 36:1115-1120

Cohen et al. Estimates and 25-year trends of the global burden of disease attributable to ambient air pollution: an analysis of data from the Global Burden of Diseases Study 2015. *Lancet* 2017; 1907-1918.

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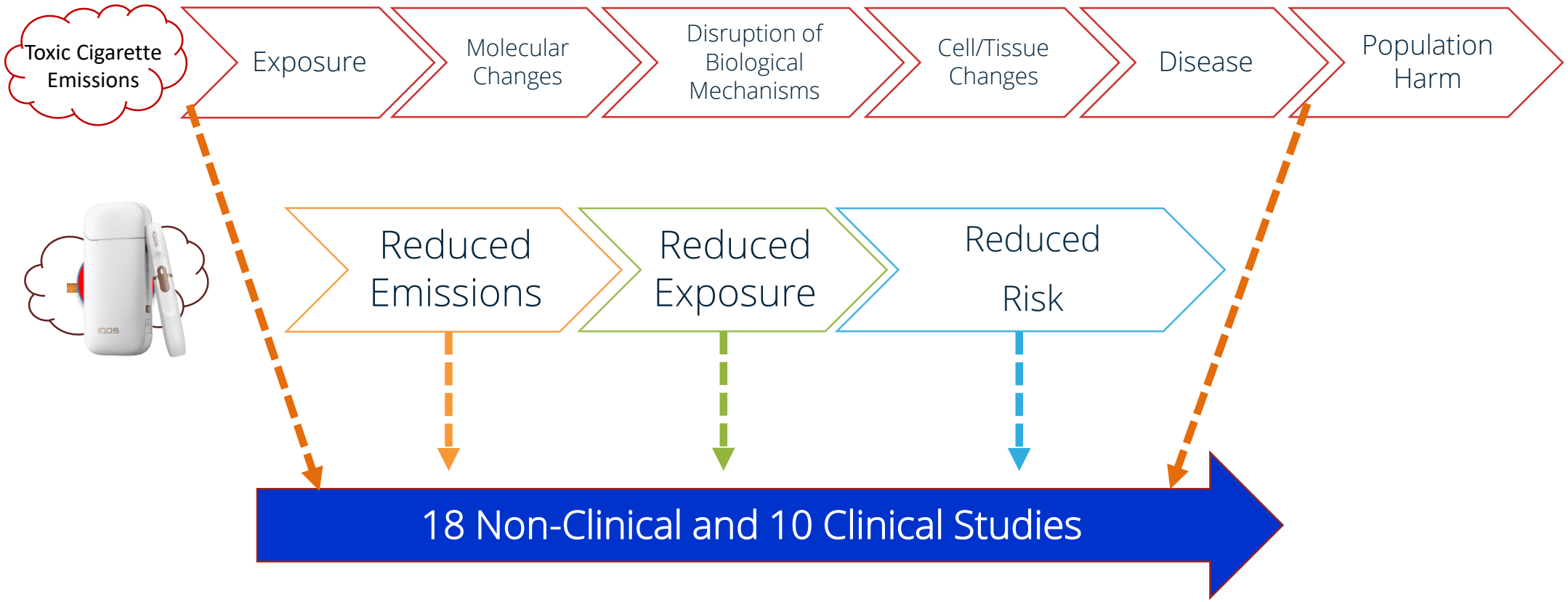
How We Assessed It

Assessing Risk Reduction



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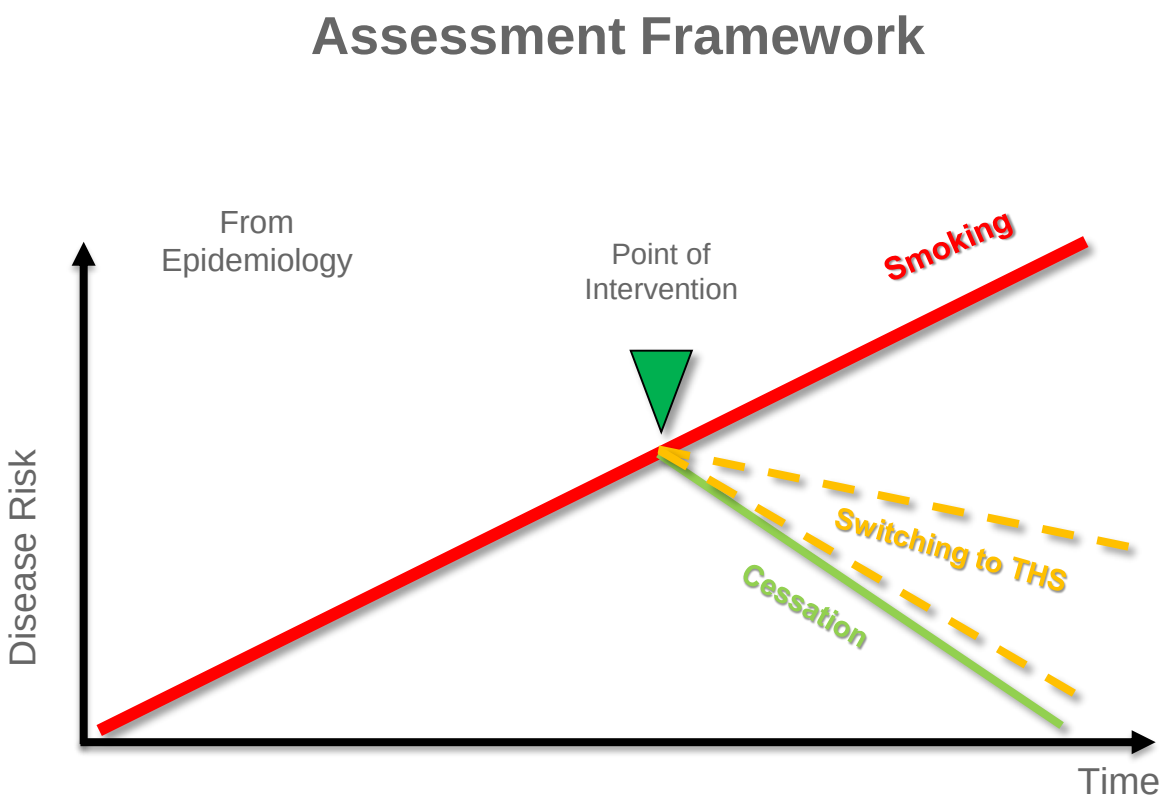
PMI's Scientific Assessment Approach



The descriptions in this chart are for illustrative purposes only

- Post-Market Studies and Surveillance
- Consumer Perception and Behavior Assessment
- Clinical Trials
- Systems Toxicology Assessment
- Standard Toxicology Assessment
- Aerosol Chemistry and Physics
- Product Design and Control Principles

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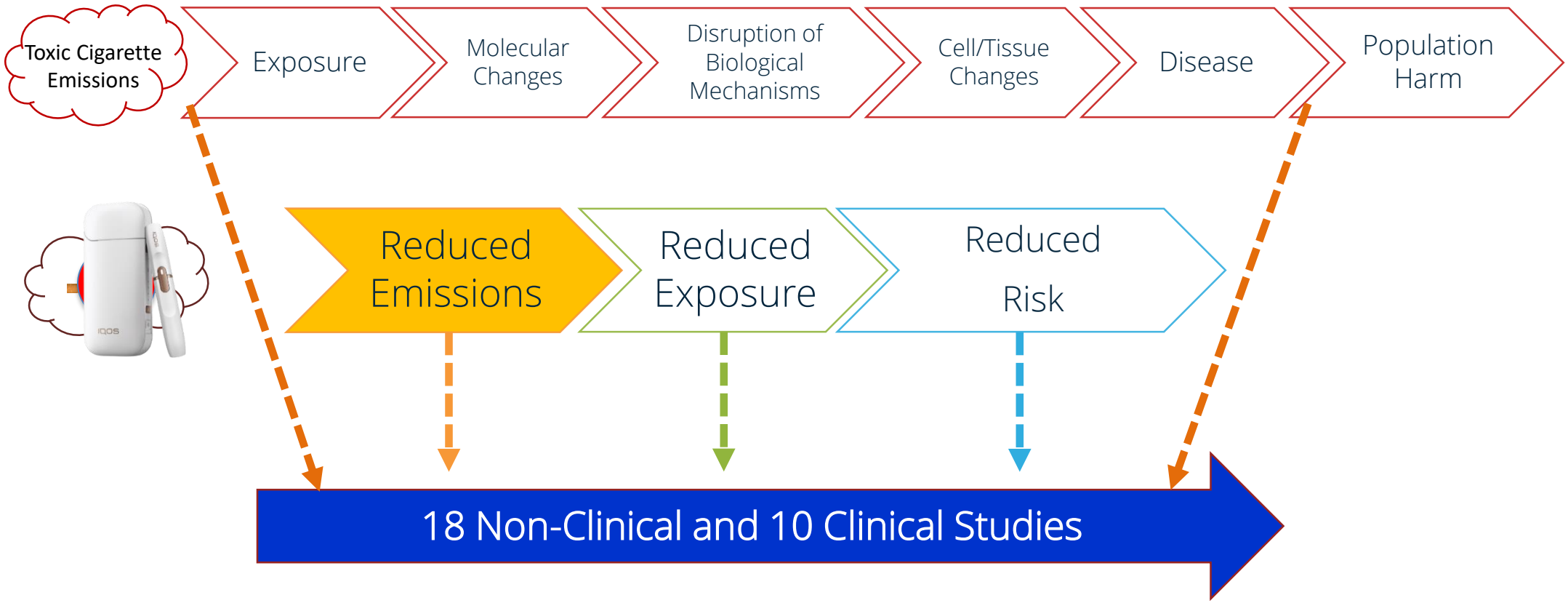
Source: Smith, M.R., *et al*., Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program. *Regulatory Toxicology and Pharmacology* (2016). http://dx.doi.org/10.1016/j.yrtph.2016.07.006

Assessing Risk Reduction - Reduced Emissions



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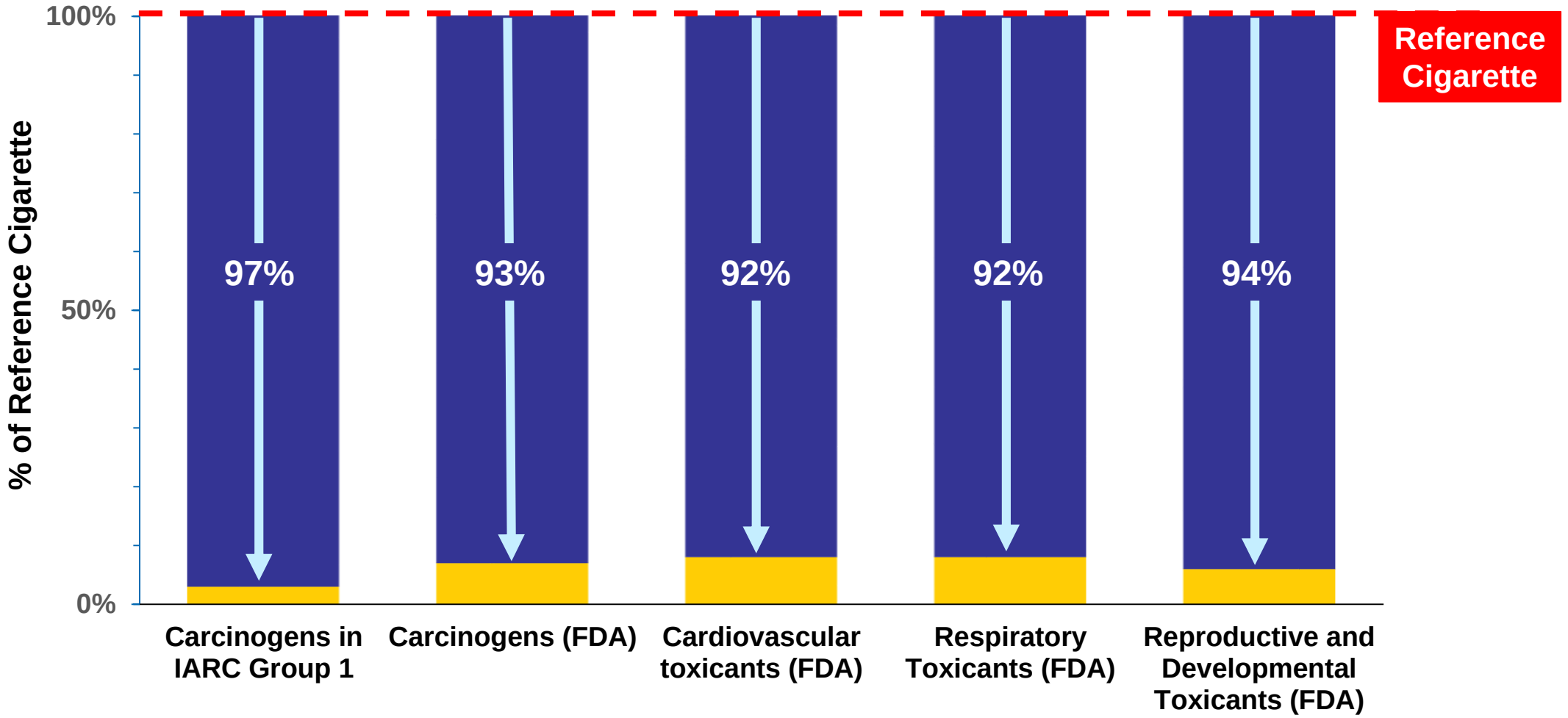
Reductions of Toxicants by Disease Category



Number of toxicants	12	29	8	18	7

Note: Intense Health Canada's Smoking Regime; Comparison on a per-stick basis; Excludes Nicotine

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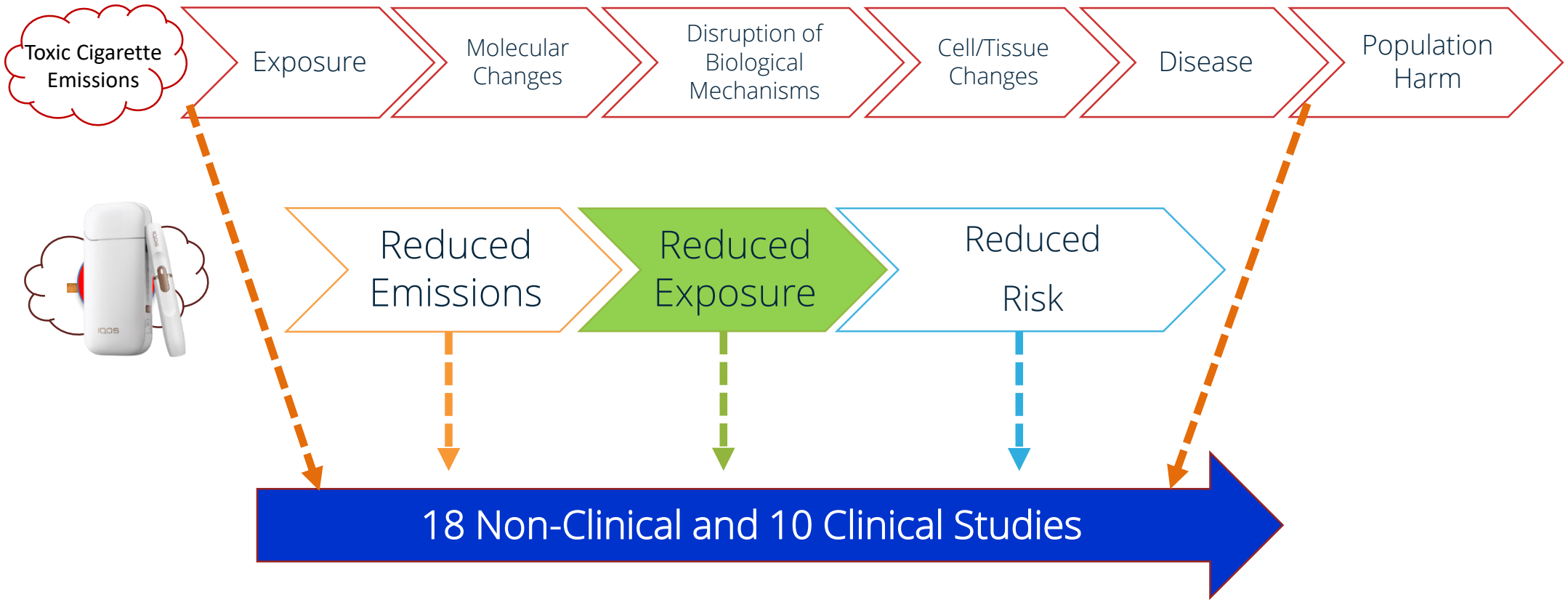
Assessing Risk Reduction - Reduced Exposure



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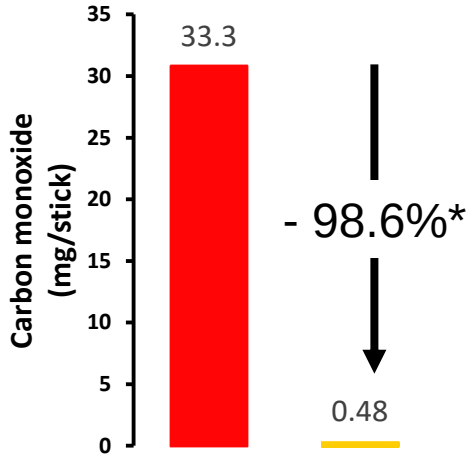
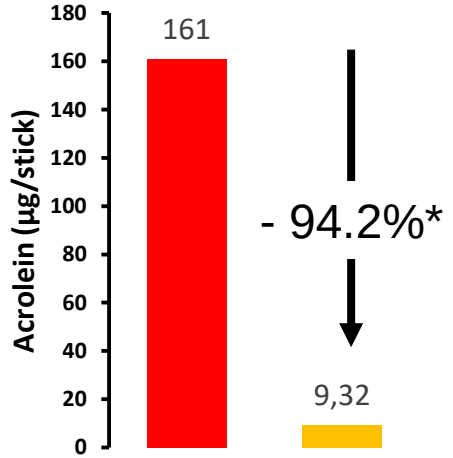
Changes in Exposure to HPHCs with THS Use

Reduced Exposure in Healthy Human Subjects

HPHCs Are Drastically Reduced in THS Aerosol





Leads to

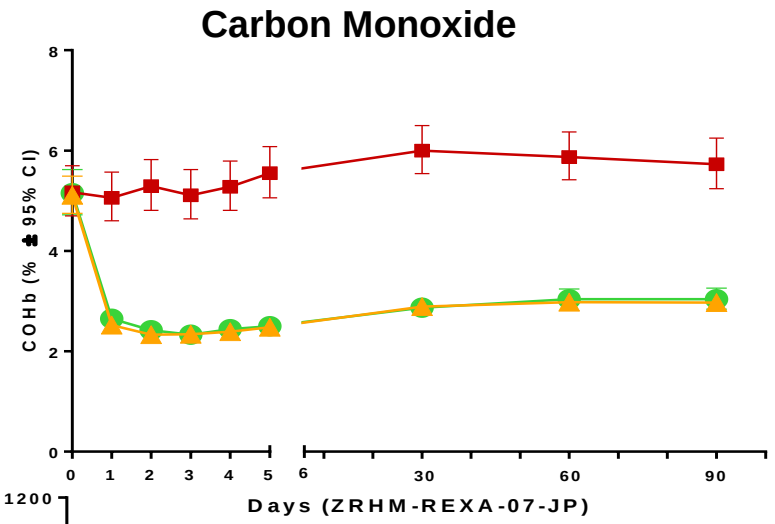
Cigarette

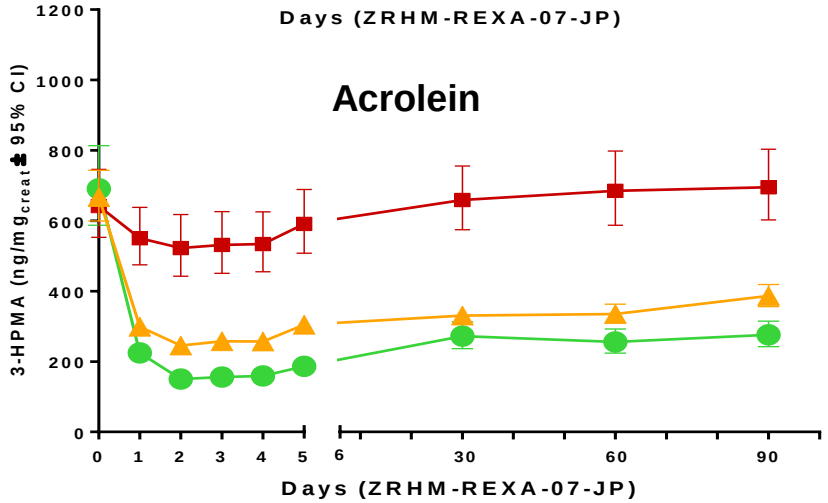
THS

Smoking Abstinence

Leads to

Exposure Is Significantly Reduced After Switching to THS





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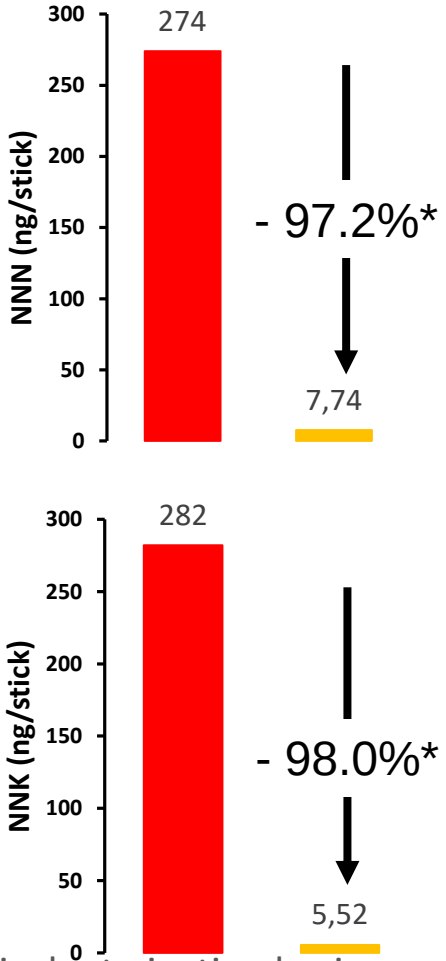

Leads to

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Smoking Abstinence

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www.pmiscience.com

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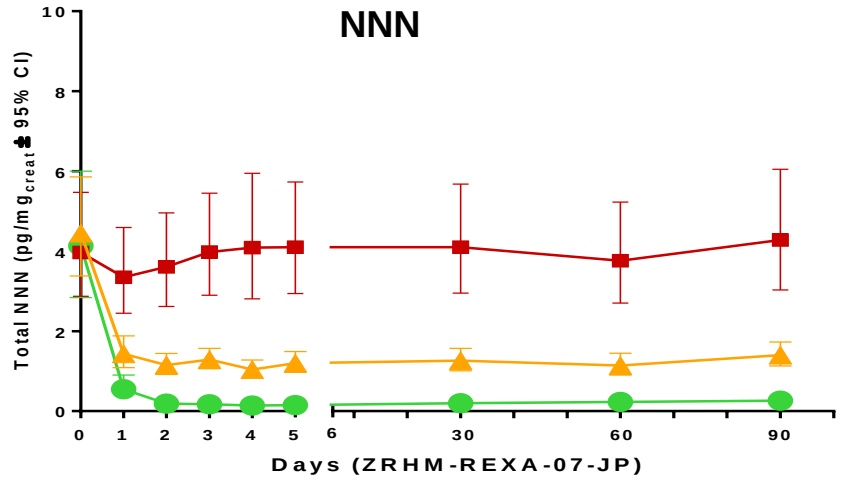
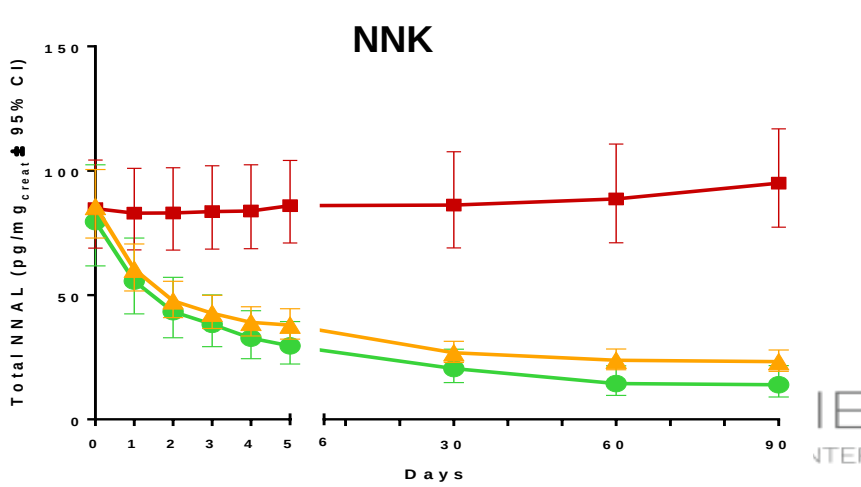
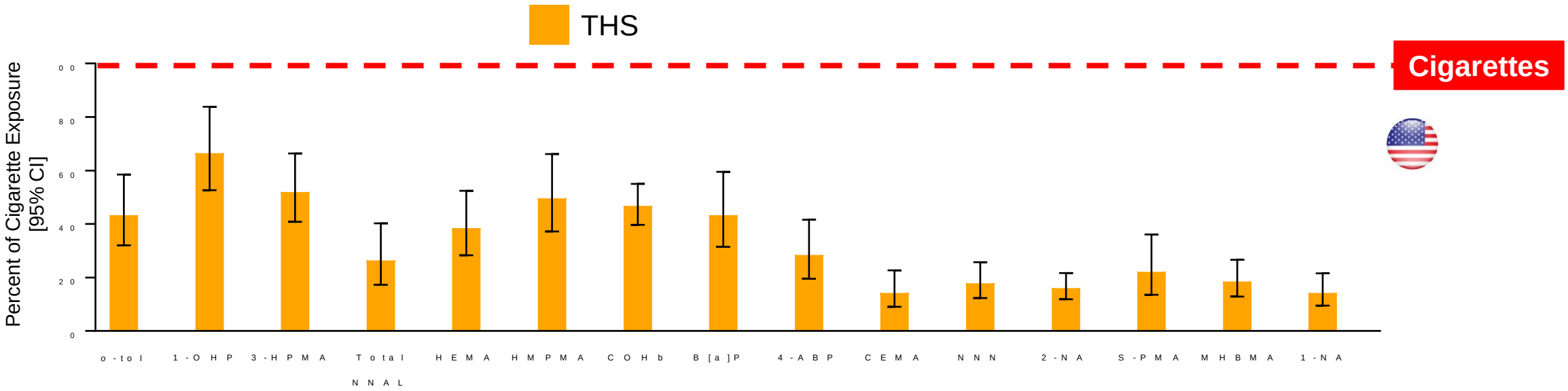


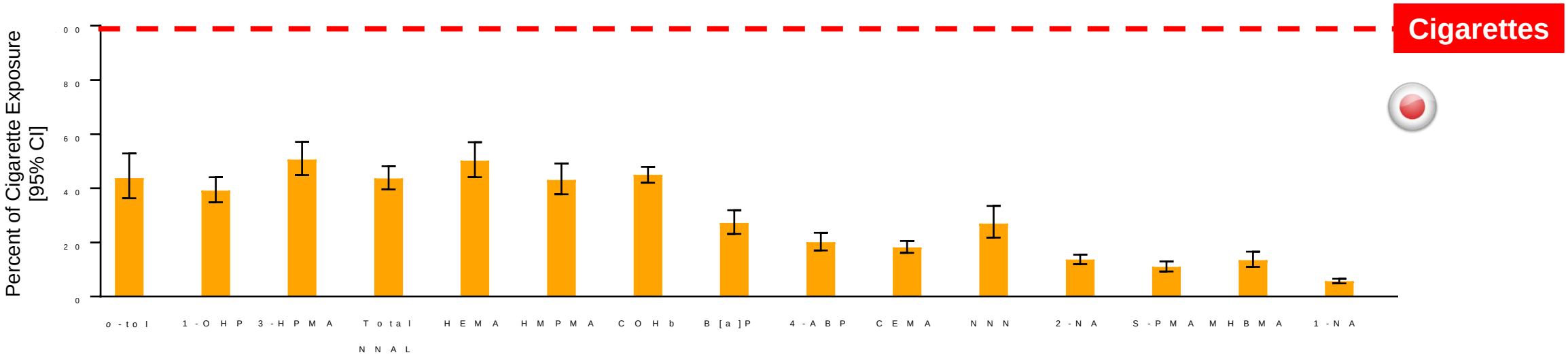


* On equivalent nicotine basis

Reduced Exposure Compared with Cigarettes

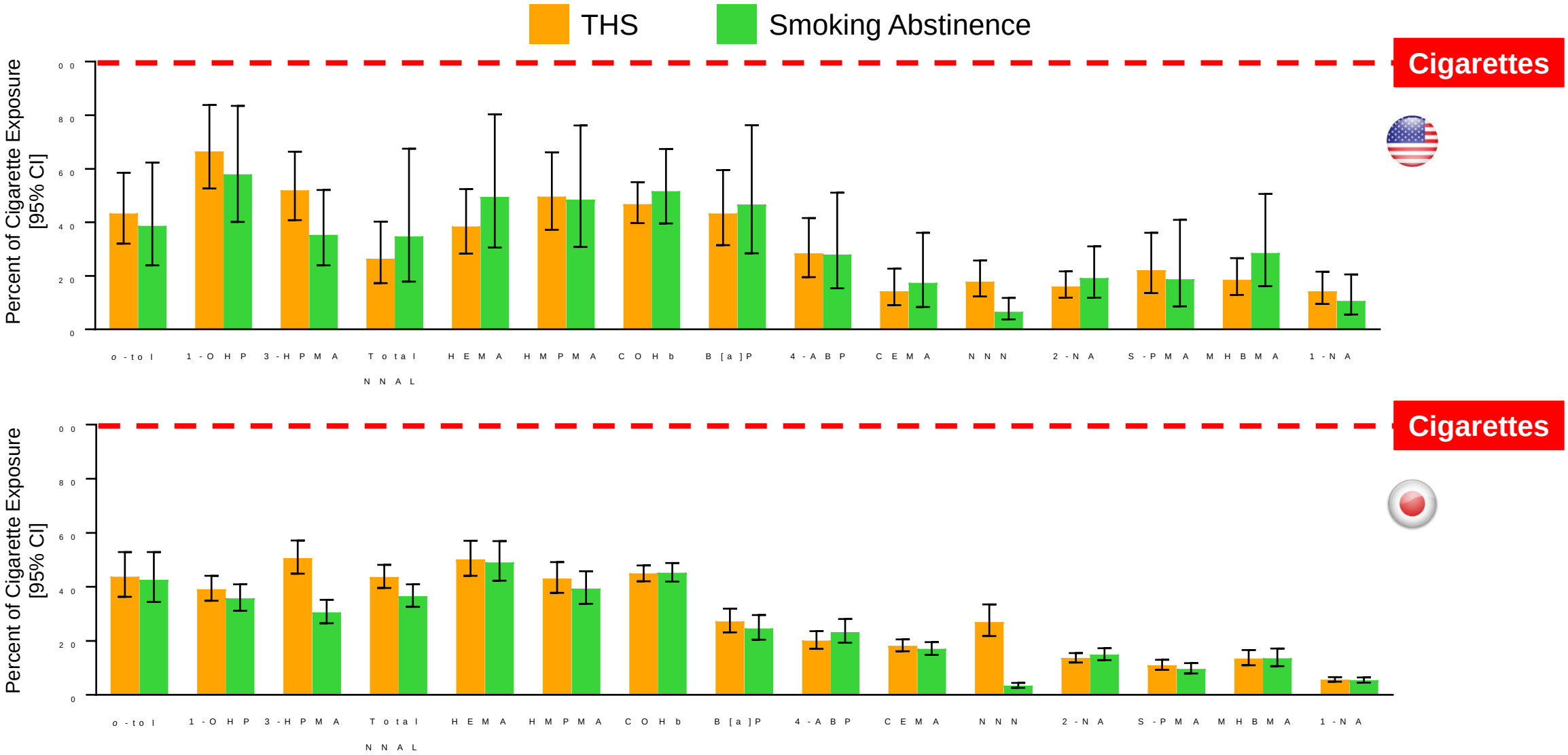
Reduced Exposure in Healthy Human Subjects





Reduced Exposure Similar to Smoking Abstinence

Reduced Exposure in Healthy Human Subjects



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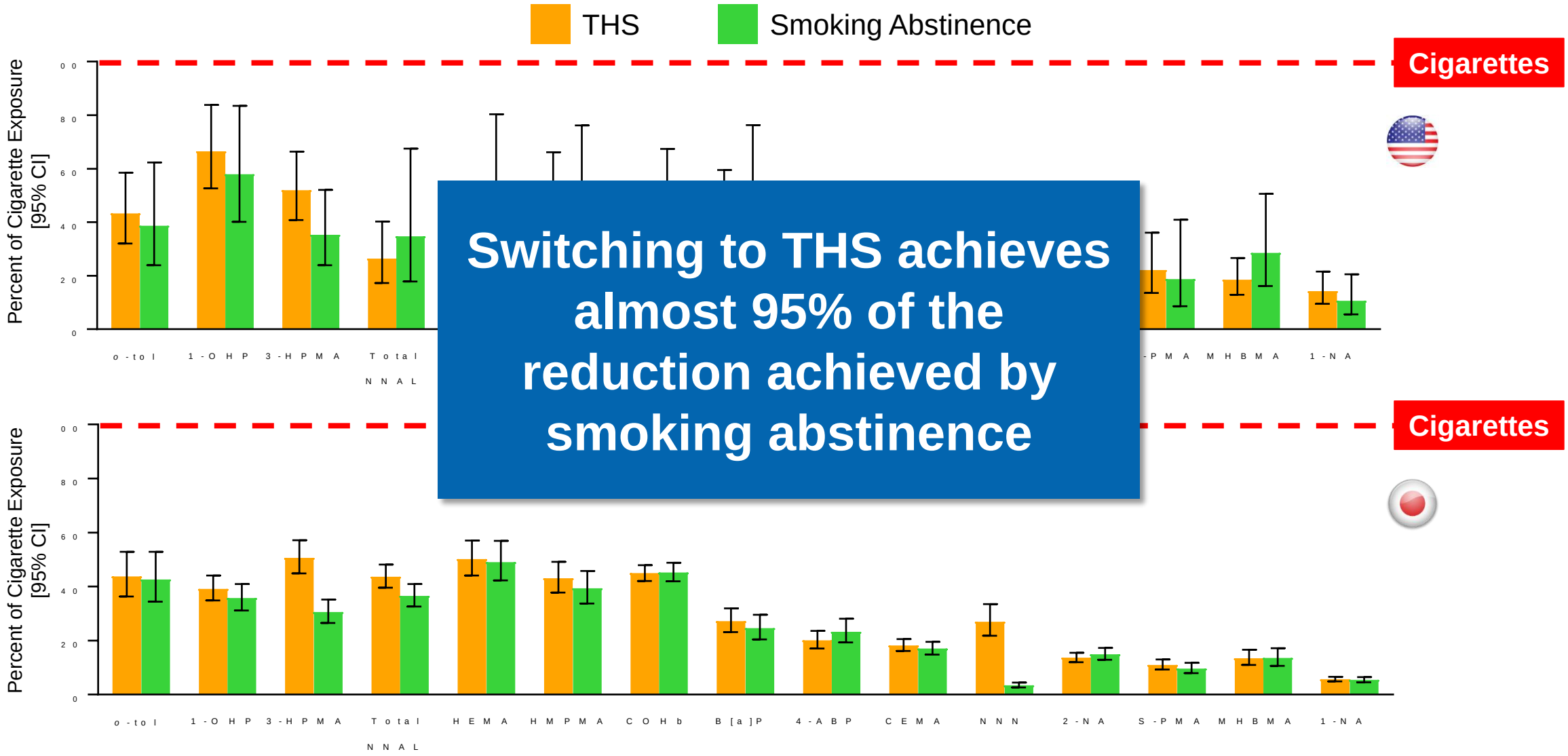
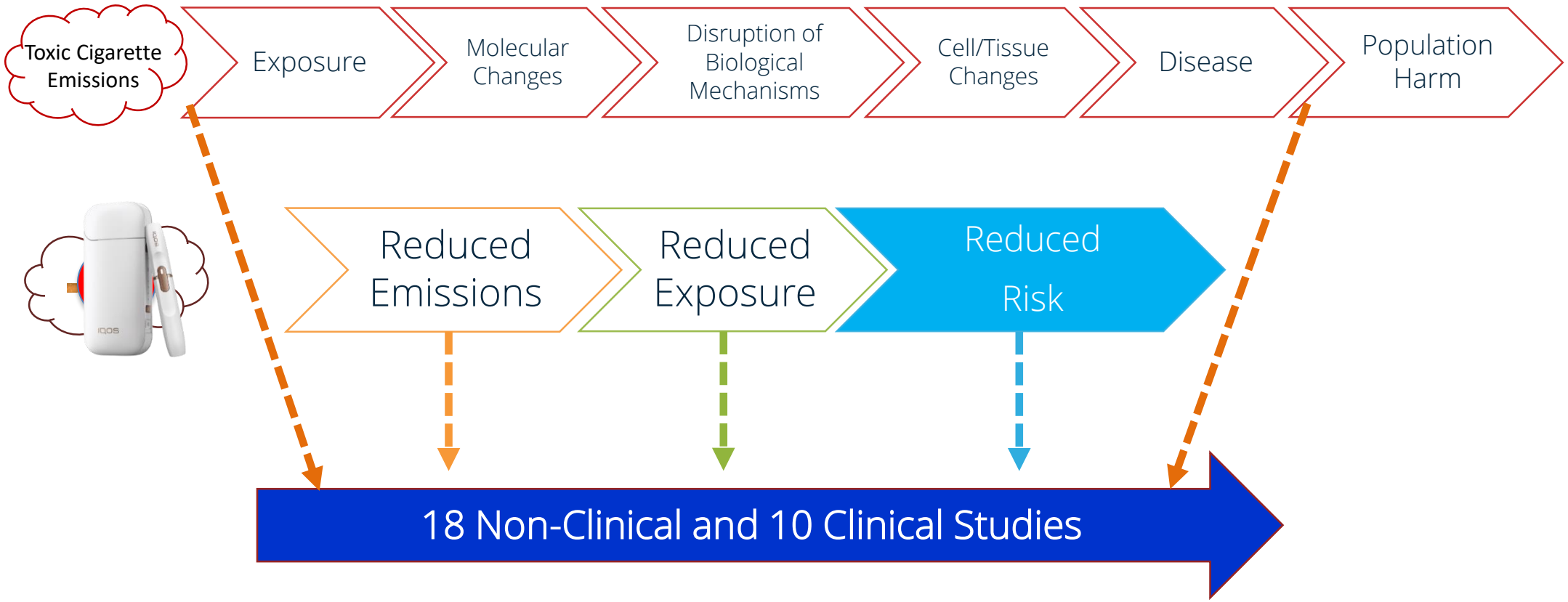


Assessing Risk Reduction - Reduced Adverse Health Effects



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Exposure Response Study

Improvements in Clinical Risk Endpoints After Six Months

Pathomechanisms	Co-Primary Endpoints	Type of Change	Observed Change*	Halperin-Rüger Adjusted CI	1-Sided *p*-Value (0.0156)	THS Directional Change vs. SA (Literature)
Lipid Metabolism	**HDL-C**	Difference	3.09 mg/dL	1.10, 5.09	<0.001**	✓ Significant
Inflammation	**WBC Count**	Difference	–0.420 GI/L	–0.717, –0.123	0.001 **	✓ Significant
Endothelial Function	**sICAM-1**	% Reduction	2.86 %	–0.426, 6.04	0.030	✓
Clotting	**11-DTX-B2**	% Reduction	4.74 %	–7.50, 15.6	0.193	✓
Oxidative Stress	**8-epi-$PGF_{2\alpha}$**	% Reduction	6.80 %	–0.216, 13.3	0.018	✓
Acute Effects	**COHb**	% Reduction	32.2 %	24.5, 39.0	<0.001**	✓ Significant
Lung Function	**FEV_1 %pred**	Difference	1.28 %pred	0.145, 2.42	0.008 **	✓ Significant
Genotoxicity	**Total NNAL**	% Reduction	43.5 %	33.7, 51.9	<0.001 **	✓ Significant

- All CREs shifted in the same direction as the smoking cessation effect observed in the literature
- 5 out of 8 CREs were statistically significant compared with continued smoking

Notes:
* Observed change presented as LS Mean Difference / Relative Reduction
** Denotes significant p-value at the 1.5625% level, following test multiplicity adjustment using the Hailperin-Rüger approach
These data alone do not represent a claim of reduced risk.
THS stands for Tobacco Heating System version 2.2

Registered on clinicaltrials.gov: NCT02396381

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Increasing Number of Third-Party Studies

Aerosol Chemistry

- Committee on Toxicology (COT)
- Public Health England (PHE)
- British American Tobacco
- National Tobacco Quality Supervision and Test Center
- Federal Institute for Risk Assessment (BfR)
- University of Bern
- National Institute of Public Health
- Food & Drug Administration
- Onassis Cardiac Surgery Center
- National Institute for Public Health and the Environment (RIVM)

Indoor Air Quality

- Fondazione IRCCS Istituto Tumori
- Sapienza University
- Medved Research Center of Preventing Toxicology, Food and Chemical Safety

Pre-Clinical

- British American Tobacco
- UCSF

Clinical

- Kazan Federal University
- British American Tobacco
- National Scientific Centre "M.D. Strazhesco Institute of Cardiology"

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Scientific Substantiation Results to Date

The totality of the scientific evidence on THS 2.2 demonstrates that it presents less risk of harm to individual adult smokers. MRTP and PMTA applications filed with the U.S. FDA.

Totality of Scientific Evidence Supporting Reduced Risk Potential

- No combustion
- Reduced toxicant formation
- Reduced toxicity
- Reduced exposure
- Reversal of clinical risk endpoints
- Pre-market perception & behavior assessment
- Validated Population Health Impact Model

Reduced Impact on Users and Those Around Them

- Less smell
- No ash
- No risk of burning
- No negative impact on indoor air quality

Improved Oral Hygiene

- Better breath
- Less unpleasant after taste
- Reduced tooth staining

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THANK YOU!